(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 April 2003 (03.04.2003)

PCT

(10) International Publication Number
WO 03/026647 A1

(51) International Patent Classification[7]: A61K 31/415, C07D 231/06, 401/12, A61K 31/4155, C07D 401/06

(21) International Application Number: PCT/EP02/10433

(22) International Filing Date:
17 September 2002 (17.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
01203850.1 21 September 2001 (21.09.2001) EP

(71) Applicant *(for all designated States except US)*: SOLVAY PHARMACEUTICALS B.V. [NL/NL]; C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: KRUSE, Cornelis, G. [NL/NL]; Solvay Pharmaceuticals B.V., c/o C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). LANGE, Josephus, H.M. [NL/NL]; Solvay Pharmaceuticals B.V., c/o C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). TIPKER, Jacobus [NL/NL]; Solvay Pharmaceuticals B.V., c/o C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). HERREMANS, Arnoldus, H.J. [NL/NL]; Solvay Pharmaceuticals B.V., c/o C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL). VAN STUIVENBERG, Herman, H. [NL/NL]; Solvay Pharmaceuticals B.V., c/o C.J. van Houtenlaan 36, NL-1381 CP Weesp (NL).

(74) Agent: MUIS, Maarten; OCTROOIBUREAU ZOAN B.V., P.O. Box 140, NL-1380 AC Weesp (NL).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

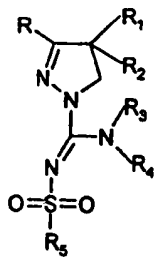
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/026647 A1

(54) Title: NOVEL 4,5-DIHYDRO-1H-PYRAZOLE DERIVATIVES HAVING CB1-ANTAGONISTIC ACTIVITY



(I)

(57) Abstract: The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives which are potent cannabinoid (CB1) receptor antagonists with utility for the treatment of diseases connected with disorders of the cannabinoid system. The compounds have the general formula (I) wherein the symbols have the meanings given in the specification. The invention also relates to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

Novel 4,5-dihydro-1H-pyrazole derivatives having CB_1-antagonistic activity

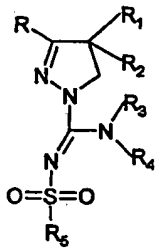
The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

The above mentioned 4,5-dihydro-1H-pyrazoles are potent cannabinoid (CB_1) receptor antagonists with utility for the treatment of diseases connected with disorders of the cannabinoid system.

Cannabinoids are present in the Indian hemp *Cannabis sativa* and have been used as medicinal agents for centuries (Mechoulam, R. and Feigenbaum, J.J. *Prog. Med. Chem.* **1987**, *24*, 159). However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on cannabinoid receptors and their (endogenous) agonists and antagonists. The discovery and the subsequent cloning of two different subtypes of Cannabinoid receptors (CB_1 and CB_2) stimulated the search for novel cannabinoid receptor antagonists (Munro, S. *et al., Nature* **1993**, *365*, 61. Matsuda, L.A. and Bonner, T.I. *Cannabinoid Receptors,* Pertwee, R.G. Ed. **1995**, 117, Academic Press, London). In addition, pharmaceutical companies became interested in the development of cannabinoid drugs for the treatment of diseases connected with disorders of the cannabinoid system (Consroe, P. *Neurobiology of Disease* **1998**, *5*, 534. Pop, E. *Curr. Opin. In CPNS Investigational Drugs* **1999**, *1*, 587. Greenberg, D.A. *Drug News Perspect.* **1999**, *12*, 458. Pertwee, R.G., *Progress in Neurobiology* **2001**, *63,* 569). Hitherto, several CB_1 receptor antagonists are known. Sanofi disclosed their diarylpyrazole congeners as selective CB_1 receptor antagonists. A representative example is SR-141716A (Dutta, A.K. *et al., Med. Chem. Res.* **1994**, *5*, 54. Lan, R. *et al., J. Med. Chem.* **1999**, *42*, 769. Nakamura-Palacios, E.M. *et al., CNS Drug Rev.* **1999**, *5*, 43). CP-272871 is a pyrazole derivative, like SR141716A, but less potent and less CB_1 receptor subtype-selective than SR141716A (Meschler, J. P. *et al., Pharmacol.* **2000**, *60,* 1315). Aminoalkylindoles have been disclosed as CB_1 receptor antagonists. A representative example is Iodopravadoline (AM-630), which was introduced in 1995. AM-630 is a moderately active CB_1 receptor antagonist, but sometimes behaves as a weak partial agonist (Hosohata, K. *et al., Life Sc.* **1997**, *61*, PL115). Researchers from Eli Lilly described aryl-aroyl substituted benzofurans as selective CB_1 receptor antagonists (*e.g.* LY-320135) (Felder, C.C. *et al., J. Pharmacol. Exp. Ther.* **1998**, *284,* 291). 3-Alkyl-5,5'-diphenylimidazolidinediones were described as cannabinoid receptor ligands, which were indicated to be cannabinoid antagonists (Kanyonyo, M. *et al., Biorg. Med.Chem. Lett.* **1999**, *9,* 2233). Aventis Pharma claimed diarylmethyleneazetidine analogs as CB_1 receptor antagonists (Mignani, S. *et al.,* Patent FR 2783246, 2000; *Chem. Abstr.* **2000**, *132,* 236982). Tricyclic pyrazoles were claimed by Sanofi-Synthelabo as CB_1 antagonists (Barth, F. *et al., Chem. Abstr.* **2001**, *134,* 340504). Interestingly, many CB_1 receptor antagonists have been

reported to behave as inverse agonists *in vitro* (Landsman, R.S. *et al., Eur. J. Pharmacol.* **1997**, *334*, R1). Reviews provide a nice overview of the cannabinoid research area (Mechoulam, R. *et al., Prog. Med. Chem.* **1998**, *35*, 199. Lambert, D.M. *Curr. Med. Chem.* **1999**, *6*, 635. Mechoulam, R. *et al., Eur. J. Pharmacol.* **1998**, *359*, 1. Williamson, E. M. and Evans, F. J. *Drugs* **2000**, *60*, 1303. Pertwee, R. G. *Addiction Biology* **2000**, *5*, 37. Robson, P. *Br. J. Psychiatry* **2001**, *178*, 107. Pertwee, R. G. *Prog. Neurobiol.* **2001**, *63*, 569. Goya, P; Jagerovic, N. *Exp. Opin. Ther. Patents* **2000**, *10*, 1529. Pertwee, R. G. *Gut* **2001**, *48*, 859).

It has now surprisingly been found that potent and selective antagonism of cannabinoid-CB_1 receptors is present in the novel 4,5-dihydro-1H-pyrazole derivatives of the formula (I), prodrugs thereof, tautomers thereof and salts thereof



(I)

wherein

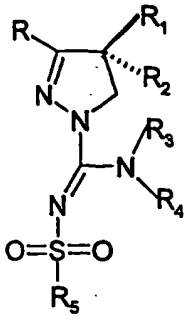
- R and R_1 independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2, 3 or 4 substituents Y, which can be the same or different, from the group C_{1-3}-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C_{1-2})-amino, mono- or dialkyl (C_{1-2})-amido, (C_{1-3})-alkyl sulfonyl, dimethylsulfamido, C_{1-3}-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R and/or R_1 represent naphtyl,
- R_2 represents hydrogen, hydroxy, C_{1-3}-alkoxy, acetyloxy or propionyloxy,
- R_3 represents a hydrogen atom or a branched or unbranched C_{1-8} alkyl group or a C_{3-7} cycloalkyl group which alkyl group or cycloalkyl group may be substituted with a hydroxy group,
- R_4 represents a C_{2-10} branched or unbranched heteroalkyl group, C_{3-8} non-aromatic heterocycloalkyl group or C_{4-10} non-aromatic heterocycloalkyl-alkyl group which groups contain one or more heteroatoms from the group (O, N, S) or a $-SO_2-$ group, which C_{2-10} branched or unbranched heteroalkyl group, C_{3-8} non-aromatic heterocycloalkyl group or C_{4-10} non-aromatic heterocycloalkyl-alkyl group may be substituted with a keto group, trifluoromethyl group, C_{1-3} alkyl group, hydroxy, amino, monoalkylamino, or dialkylamino group or a fluoro atom, or R_4 represents an amino, hydroxy, phenoxy or benzyloxy group, or R_4 represents a C_{1-8} alkoxy, C_{3-8} alkenyl, C_{5-8} cycloalkenyl or C_{6-8} cycloalkenylalkyl

group which groups may contain a sulphur, nitrogen or oxygen atom, a keto group or $-SO_2-$ group, which alkoxy, alkenyl and cycloalkenyl groups may be substituted with a hydroxy group, a trifluoromethyl group, an amino group, a monoalkylamino group or dialkylamino group or a fluoro atom, or R_4 represents a C_{2-5} alkyl group which alkyl group contains a fluoro atom, or R_4 represents an imidazolylalkyl group, benzyl, pyridylmethyl, phenethyl or thienyl group, or R_4 represents a substituted phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl group wherein the aromatic rings are substituted with 1, 2 or 3 of the substituents Y, wherein Y has the meaning as indicated above,

or when R_3 is H or methyl, R_4 may represent a group NR_6R_7 wherein

- R_6 and R_7 are the same or different and represent C_{2-4} alkyl , C_{2-4} trifluoroalkyl or R_6 represents a methyl group with the proviso that R_7 represents a C_{2-4} alkyl group, or R_6 and R_7 - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated heterocyclic moiety having 4 to 8 ring atoms which heterocyclic moiety may contain an oxygen or sulphur atom or a keto group or $-SO_2-$ group or an additional nitrogen atom, which saturated or unsaturated heterocyclic moiety may be substituted with a C_{1-4} alkyl group, or
- R_3 and R_4 together with the nitrogen atom to which they are bonded form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms, which heterocyclic moiety may contain one or more atoms from the group (O, N, S) or a keto group or $-SO_2-$ group, which moiety may be substituted with a C_{1-4} alkyl, hydroxyalkyl, phenyl, thienyl, pyridyl, amino, monoalkylaminoalkyl, dialkylaminoalkyl, monoalkylamino, dialkylamino, aminoalkyl, azetidinyl, pyrrolidinyl, piperidinyl or hexahydro-1H-azepinyl group,
- R_5 represents benzyl, phenyl, thienyl or pyridyl which may be substituted with 1, 2, 3 or 4 substituents Y, wherein Y has the meaning as indicated above, which can be the same or different, or R_5 represents C_{1-8} branched or unbranched alkyl, C_{3-8} alkenyl, C_{3-10} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl or C_{5-8} cycloalkenyl or R_5 represents naphtyl.

At least one centre of chirality is present (at the C_4 position of the 4,5-dihydro-1H-pyrazole moiety) in the compounds of the formula (I). The invention relates both to racemates, mixtures of diastereomers and the individual stereoisomers of the compounds having formula (I). Particular compounds of interest of formula (I) have the absolute stereoconfiguration at the C_4 position of the 4,5-dihydro-1H-pyrazole moiety as represented by formula (1^B).



(1a)

The invention also relates both to the E isomer, Z isomer and E/Z mixtures of compounds having formula (I).

The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

Due to the potent CB_1 antagonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetence, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelinisation related disorders, as well as for the treatment of pain disorders, including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders.

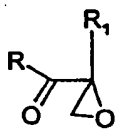
The affinity of the compounds of the invention for cannabinoid CB_1 receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabinoid CB_1 receptor is stably transfected in conjunction with [^{3}H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [^{3}H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

The cannabinoid CB_1 antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB_1

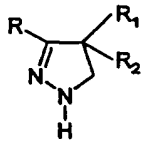
receptors are stably expressed. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB_1 receptors by CB_1 receptor agonists (*e.g.* CP-55,940 or (R)-WIN-55,212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration-dependent manner. This CB_1 receptor-mediated response can be antagonised by CB_1 receptor antagonists such as the compounds of the invention.

Intermediates having formula (II) (see below) can be obtained according to methods known, for example: a) Francotte, E. and Tong, Z. *Chem. Abstr.* **126**, 213598; b) Rempfler, H. and Kunz, W. *Chem. Abstr.* **113**, 40432; c) Rempfler, H. and Kunz, W. *Chem. Abstr.* **107**, 217473.
Intermediates having formula (III) (see below), wherein R_2 represents hydrogen can be obtained according to methods known, for example: a) EP 0021506; b) DE 2529689; c) Grosscurt, A.C. *et al., J. Agric. Food Chem.* **1979**, 27, (2), 406.

Intermediates having formula (III) (see below), wherein R_2 represents a hydroxy group can be obtained by reacting of a compound having formula (II)


(II)

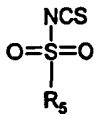
with hydrazine or hydrazine hydrate. This reaction is preferably carried out in an organic solvent, for example ethanol, and yields a compound having formula (III)


(III)

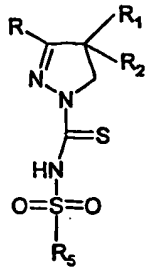
Suitable synthetic routes for the compounds of the invention are the following:

Synthetic route A1

Step 1: reaction of a compound having formula (III) with a thioisocyanate derivative having formula (IV),


(IV)

preferably carried out in an organic solvent, for example acetonitrile. This reaction gives a thiocarboxamide derivative having formula (V), wherein R, R_1, R_2 and R_5 have the meanings as described above for compound (I).

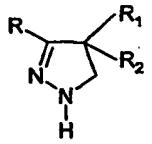


(V)

Step 2: reaction of a compound having formula (V) with a compound R_3R_4NH in the presence of a mercury(II) salt, such as for example $HgCl_2$, gives a compound having formula (I). This reaction is preferably carried out in an organic solvent, such as for example acetonitrile.

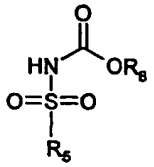
Synthetic route A2

Step 1: reaction of a compound having formula (III)



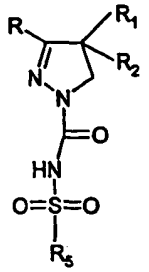
(III)

with a carbamate ester derivative having formula (VI).



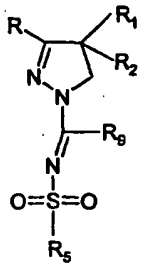
(VI)

wherein R_8 represents a lower alkyl group, for example methyl. This reaction is preferably carried out in an organic solvent, for example 1,4-dioxane, and yields a 4,5-dihydropyrazole-1-carboxamide derivative having formula (VII), wherein R, R_1, R_2 and R_5 have the meanings as described above for compound (I).



(VII)

Step 2: reaction, preferably carried out in an inert organic solvent, for example chlorobenzene, of a compound having formula (VII) with a halogenating agent such as PCl_5, gives a 4,5-dihydropyrazole-1-carboximidoyl halogenide derivative having formula (VIII) wherein R, R_1, R_2, R_5 have the meanings as described above for compound (I) and wherein R_8 represents a halogen atom, for example Cl.



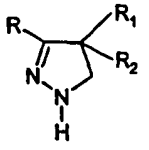
(VIII)

Step 3: reaction of a compound having formula (VIII) with a compound R_3R_4NH preferably carried out in an inert organic solvent, such as for example dichloromethane gives a compound having formula (I).

Alternatively, compounds R_3R_4NH which contain an additional nucleophilic nitrogen atom are reacted with a compound having formula (VIII) in such a way that the abovementioned additional nucleophilic nitrogen atom is protected by a protective group, for example a t-butoxycarbonyl (Boc) group and the like. Subsequent removal of the protective group according to known methods yields a compound having formula (I). *(See for example: T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", third edition, John Wiley & Sons, Inc., New York, 1999).*

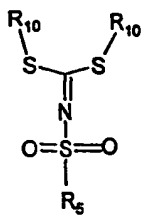
Synthetic route A3

Step 1: reaction of a compound having formula (III)



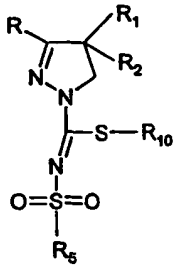
(III)

with a dithioimidocarbonic ester derivative having formula (IX) .



(IX)

wherein R_{10} represents a C_{1-3} alkyl group. This reaction is preferably carried out in an organic solvent, for example acetonitrile or toluene, and yields a carboximidothioic ester derivative having formula (X), wherein R, R_1, R_2, R_5 have the meanings as described above for compound (I) and wherein R_{10} represents a C_{1-3} alkyl group.



(X)

Alternatively, a compound having formula (X) can be obtained from the reaction of a compound having formula (V) with a compound R_{10}-X, wherein X represents a leaving group such as an iodide group, and R_{10} has the meaning as described above for (X).

Step 2: Reaction, preferably carried out in an organic solvent, such as methanol, of a compound having formula (X) with a compound R_3R_4NH gives a compound having formula (I).

The preparation of the compounds is illustrated in the following examples.

Example 1

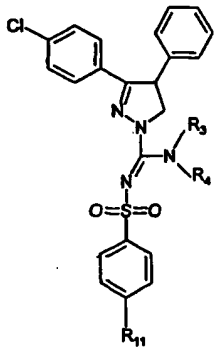
3-(4-Chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-N-(piperidin-1-yl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine

Part A: To a solution of N-((4-chlorophenyl)sulfonyl)carbamic acid methyl ester (CAS: 34543-04-9) (2.99 gram, 12.0 mmol) and pyridine (4 mL) in 1,4-dioxane (20 mL) is added 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (3.39 gram, 13.2 mmol) and the resulting mixture is stirred for 4 hours at 100 °C. After concentration *in vacuo* the residue is dissolved in dichloromethane, successively washed with water, 1N HCl and water, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to a volume of 20 mL. Methyl-tert-butyl ether (60 mL) is added and the resulting solution is concentrated to a volume of 20 mL. The formed crystals are collected by filtration and recrystallised from methyl-*tert*-butyl ether to give 3-(4-chlorophenyl)-N-((4-

chlorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (4.75 gram, 76 % yield) Melting point: 211-214 °C.

Part B: A mixture of 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1.42 gram, 3.00 mmol) and phosphorus pentachloride (PCl_5) (0.63 gram, 3.03 mmol) in chlorobenzene (15 mL) is heated at reflux temperature for 1 hour. After thorough concentration *in vacuo*, the formed 3-(4-chlorophenyl)-N-((4-chlorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidoyl chloride is suspended in dry dichloromethane (30 mL) and reacted with 1-aminopiperidine (1.08 mL, 10.0 mmol). After stirring at room temperature for 16 hours, the mixture is twice washed with water and concentrated *in vacuo*. The residue is crystallised from methyl-t-butyl ether (MTBE) to give pure 3-(4-chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-N-(piperidin-1-yl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (0.57 gram, 34 % yield). Melting point (MP): 213-214 °C. MS ESI$^+$: 556 (MH^+).

Analogous to the synthesis of example 1, in total 57 compounds having formula (XI) were prepared. Those are listed below in table 1 and list 1.



(XI)

Table 1

Ex.	R_3	R_4	R_{11}	Melting point (°C)	MS ESI$^+$ (MH^+)	Salt form
2	H	Piperidin-1-yl	F	189-190	540	
3	H	Pyrrolidin-1-yl	Cl	190-195	542	
4	H	Pyrrolidin-1-yl	F		526	
5	H	azepan-1-yl	Cl	197-199		
6	H	Cis/trans-2,6-dimethylpiperidin-1-yl	Cl	110-146		
7	H	2,2,2-Trifluoroethylamino	Cl	149-151		
8	H	t-Butoxy	Cl	194-196	545	
9	H	2-Propoxy	Cl	142-145		
10	H	Methoxy	Cl		503	
11	H	Methoxy	F		487	
12	H	Morpholin-4-yl	Cl	213-216		
13	H	2-(Morpholin-4-yl)ethyl	Cl	137-139		
14	H	2-(Piperidin-1-yl)ethyl	Cl	168-169		

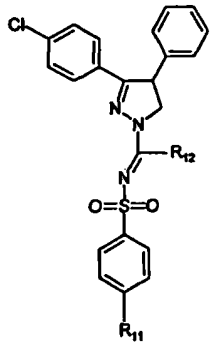
15	H	2-(Pyrrolidin-1-yl)ethyl	Cl	155-157		
16	H	2-(Dimethylamino)ethyl	F			
17	CH_3	2-(Dimethylamino)ethyl	Cl	168-170		.HCl
18	H	2-(Dimethylamino)ethyl	Cl	63-68		
19	H	2-(Methylamino)ethyl	Cl		530	.HCl
20	H	2-(Ethylamino)ethyl	Cl		544	.HCl
Ex.	**R_3**	**R_4**	**R_{11}**	**Melting point (°C)**	**MS ESI$^+$ (MH^+)**	**Salt form**
21	H	3-(Dimethylamino)-2-methylprop-2-yl	Cl		572	
22	H	(N-Methylpyrrolidin-2-yl)methyl	Cl	149-159		
23	H	(N-Methylpyrrolidin-3-yl)methyl	Cl		570	
24	H	4-(Pyrrolidin-1-yl)butyl	Cl	128-130	598	
25	H	3-(Morpholin-4-yl)propyl	Cl			
26	H	3-(Dimethylamino)propyl	Cl	221-224	558	.HCl
27	CH_3	3-(Dimethylamino)propyl	F	93 (dec.)	556	.HCl
28	C_2H_5	2-Aminoethyl	Cl			
29	H	3-(Dimethylamino)propyl	F	105-109	542	.HCl
30	H	3-(1H-Imidazol-1-yl)propyl	Cl			
31	H	2-Aminoxyethyl	Cl		532	
32	H	2-(Dimethylamino)ethoxy	Cl	201	560	
33	H	2-(Diethylamino)ethoxy	Cl	210	588	
34	H	2-(Methoxy)ethyl	Cl	99-102		
35	CH_3	2-(Acetoxy)ethyl	Cl	157-158	573	
36	H	2-Hydroxyethyl	F		501	
37	H	2-Hydroxyethyl	Cl		517	
38	H	2-Hydroxy-2-methylpropyl	Cl			
39	H	3-Hydroxypropyl	Cl	129-132		
40	CH_3	Hydroxy	Cl	208-211		
41	H	Methoxy	CF_3	178-180		
42	H	2-Fluoroethyl	Cl	100-103		
43	H	2-Fluoroethyl	CF_3	132-134		

List 1

44. 3-(4-Chlorophenyl)-N-methoxy-N'-((3-methylphenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 151-152 °C.
45. 3-(4-Chlorophenyl)-N-methoxy-N'-((2-methylphenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 145-146 °C.
46. 3-(4-Chlorophenyl)-N-methoxy-N'-((2,4,5-trifluorophenyl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 160-162 °C.
47. 3-(5-Chlorothien-2-yl)-N'-((4-chlorophenyl)sulfonyl)-N-methoxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 180-181 °C.
48. N'-((4-Chlorophenyl)sulfonyl)-3-(4-fluorophenyl)-N-methoxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 201-203 °C.

49. 3-(4-Chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-N-methoxy-4-(3-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine.MP: 80-83 °C.
50. 3-(4-Chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-N-methoxy-4-(2,6-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine.MP:174-177 °C.
51. 3-(4-Chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-N-(2-fluoroethyl)-4-(2,6-difluorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP:153-155°C.
52. 3-(4-Chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-N-(2-fluoroethyl)-4-(3-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 130 °C.
53. 3-(4-Chlorophenyl)-N-(2-fluoroethyl)-4-(3-fluorophenyl)-N'-((4-(trifluoromethyl)phenyl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 155 °C.
54. 3-(4-Chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-4-(3-fluorophenyl)-N-(methoxy)-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
55. 3-(4-Chlorophenyl)-4-(3-fluorophenyl)-N-(methoxy)-N'-((4-(trifluoromethyl)phenyl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: > 260 °C.
56. 3-(4-Chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-4-(2-fluorophenyl)-N-(methoxy)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 162-164 °C.
57. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-(methoxy)-N'-((4-(trifluoromethyl)phenyl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 147-149 °C.

In an analogous manner 29 compounds having formula (XII) were prepared. Those are listed below in table 2 and list 2.



(XII)

Table 2

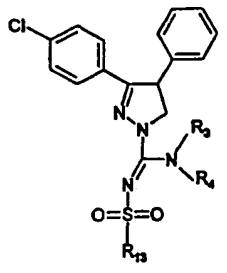
Ex.	R_{11}	R_{12}	Melting point (°C)	MS ESI$^+$ (MH^+)	Salt form
58	Cl	1,2,3,4-Tetrahydroisoquinolin-2-yl		589	
59	F	1,2,3,4-Tetrahydroisoquinolin-2-yl		573	
60	F	Pyrrolidin-1-yl		511	
61	Cl	Morpholin-4-yl		543	
62	F	Morpholin-4-yl		527	
63	Cl	Azetidin-1-yl	200-202	513	

64	F	Azetidin-1-yl		497	
Ex.	R_{11}	R_{12}	Melting point (°C)	MS ESI$^+$ (MH^+)	Salt form
65	Cl	4-Hydroxypiperidin-1-yl	112-117		
66	Cl	3-Hydroxypiperidin-1-yl	218-222		
67	Cl	4-(Hydroxymethyl)piperidin-1-yl	185-188		
68	Cl	1,1-Dioxythiomorpholin-4-yl	120	591	
69	Cl	4-Methylpiperazin-1-yl		556	
70	Cl	[1,4']-Bipiperidin-1'-yl	260	624	
71	Cl	3,5-Cis-dimethylpiperazin-1-yl			
72	F	4-Methylpiperazin-1-yl		540	
73	F	3,5-Cis-dimethylpiperazin-1-yl		554	
74	F	[1,4']-Bipiperidin-1'-yl	> 280	608	
75	F	4-Methyl-1,4-diazepan-1-yl	115	554	.HCl
76	Cl	1,4-diazepan-1-yl	84		
77	F	1,4-diazepan-1-yl			
78	Cl	2,6-Cis-dimethylpiperazin-1-yl	100 (dec.)		
79	F	4-(Dimethylamino)piperidin-1-yl	211-214		
80	F	Piperazin-1-yl	88-90		
81	Cl	4-(Pyridin-4-yl)piperazin-1-yl	224-226		
82	Cl	4-(2-Dimethylaminoethyl)piperazin-1-yl			
83	Cl	4-(3-Dimethylaminopropyl)piperazin-1-yl	163-165		
84	Cl	4-(3-Hydroxypropyl)piperazin-1-yl	> 140 (dec.)		
85	Cl	2,6-Cis-dimethyl-4-methylpiperazin-1-yl	75-80		

List 2

86. N-[(3-(4-chlorophenyl)-4-(3-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)(4-methylpiperazin-1-yl)methylene]-4-chlorobenzenesulfonamide. MP: 97-100 °C.

In an analogous manner the compounds having formula (XIII) have been prepared. Those are listed in table 3 or detailed below:



(XIII)

Table 3

Example	R_3	R_4	R_{13}	Melting	MS ESI$^+$

				point (°C)	(MH^+)
87	H	3-(Dimethylamino)propyl	CH_3	136-138	
88	H	N-Methylpiperidin-4-yl	i-C_3H_7		

Example 89

N-[(4-phenyl-3-(pyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)(4-methylpiperazin-1-yl)methylene]-4-fluorobenzenesulfonamide

Part A: 3-Pyridyl benzyl ketone (*Cf.* Burger et al., J. Am. Chem. Soc. **1950**, 72, 1988-1990), (30.2 g, 0.153 mol) is dissolved in methanol (400 mL) and acetic acid (1.5 mL), piperidine (1.5 mL) and formaline (35 mL, 37 % aqueous solution) are sucessively added. The resulting mixture is heated at reflux temperature for 210 minutes. The resulting mixture is allowed to attain room temperature and concentrated *in vacuo*. Water and 2N NaOH solution are added, followed by extraction with methyl-t-butyl ether (MTBE). The organic layer is twice washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatographic purification (eluant: MTBE) gives 2-phenyl-1-pyridin-3-yl propenone (21.4 gram, 67 % yield) as an oil. ESI-MS (MH^+) 210.

Part B: 2-Phenyl-1-pyridin-3-yl propenone (21.4 gram, 0.102 mol) is dissolved in ethanol (150 mL) and hydrazine hydrate is added (10.4 mL). The resulting mixture is heated at reflux temperature for 3 hours. The resulting mixture is allowed to attain room temperature and concentrated *in vacuo*. Water is added, followed by extraction with dichloromethane. The organic layer is washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo* to produce crude 4-phenyl-3-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole (23 g, ~100 % yield). ESI-MS (MH^+) 224.

Part C: Crude 4-phenyl-3-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole (9.81 g, 0.044 mol), [(4-chlorophenyl)sulfonyl]dithioimidocarbonic acid dimethyl ester (12.99 gram, 0.044 mol) and triethylamine (47 mL) are successively dissolved in acetonitrile. The resulting mixture is heated at reflux for 70 hours. The resulting mixture is allowed to attain room temperature and concentrated *in vacuo*. The residue is dissolved in dichloromethane. The organic layer is washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatographic purification (eluant: methanol/dichloromethane = 5/95 (v/v)) gives N-((4-chlorophenyl)sulfonyl)-4-phenyl-3-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester (7.15 gram, 35 % yield). ESI-MS (MH^+) 471.

Part D: N-((4-Chlorophenyl)sulfonyl)-4-phenyl-3-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester (1.50 gram, 0.0033 mol) is suspended in toluene (25 mL) and 4-methylpiperazine (5 mL) is added. The resulting mixture is heated at 60 °C for 70 hours. The resulting yellow solution is allowed to attain room temperature and concentrated *in vacuo*. The resulting residue is crystallised from MTBE to give N-[(4-phenyl-3-(pyridin-3-yl)-4,5-dihydro-1H-pyrazol-1-yl)(4-methylpiperazin-1-yl)methylene]-4-fluorobenzene-sulfonamide (1.39 g, 83 % yield). MP: 169-170 °C.

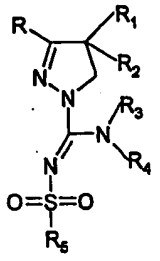
Example 90

(-)-(4S)-3-(4-Chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-N-methoxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine

(-)-(4S)-3-(4-Chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-N-methoxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine ($[\alpha^{25}_D]$ = -165 °, c = 0.01, MeOH) was obtained as an amorphous solid *via* chiral chromatographic separation of racemic 3-(4-chlorophenyl)-N'-((4-chlorophenyl)sulfonyl)-N-methoxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (Chiral stationary phase: Chiralpak AD). The mobile phase consisted of ethanol.

Claims

1. Compounds of the general formula (I)



(I)

wherein

- R and R_1 independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2, 3 or 4 substituents Y, which can be the same or different, from the group C_{1-3}-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C_{1-2})-amino, mono- or dialkyl (C_{1-2})-amido, (C_{1-3})-alkyl sulfonyl, dimethylsulfamido, C_{1-3}-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R and/or R_1 represent naphtyl,
- R_2 represents hydrogen, hydroxy, C_{1-3}-alkoxy, acetyloxy or propionyloxy,
- R_3 represents a hydrogen atom or a branched or unbranched C_{1-8} alkyl group or a C_{3-7} cycloalkyl group which alkyl group or cycloalkyl group may be substituted with a hydroxy group,
- R_4 represents a C_{2-10} branched or unbranched heteroalkyl group, C_{3-8} non-aromatic heterocycloalkyl group or C_{4-10} non-aromatic heterocycloalkyl-alkyl group which groups contain one or more heteroatoms from the group (O, N, S) or a $-SO_2-$ group, which C_{2-10} branched or unbranched heteroalkyl group, C_{3-8} non-aromatic heterocycloalkyl group or C_{4-10} non-aromatic heterocycloalkyl-alkyl group may be substituted with a keto group, trifluoromethyl group, C_{1-3} alkyl group, hydroxy, amino, monoalkylamino, or dialkylamino group or a fluoro atom, or R_4 represents an amino, hydroxy, phenoxy or benzyloxy group, or R_4 represents a C_{1-8} alkoxy, C_{3-8} alkenyl, C_{5-8} cycloalkenyl or C_{6-9} cycloalkenylalkyl group which groups may contain a sulphur, nitrogen or oxygen atom, a keto group or $-SO_2-$ group, which alkoxy, alkenyl and cycloalkenyl groups may be substituted with a hydroxy group, a trifluoromethyl group, an amino group, a monoalkylamino group or dialkylamino group or a fluoro atom, or R_4 represents a C_{2-5} alkyl group which alkyl group contains a fluoro atom, or R_4 represents an imidazolylalkyl group, benzyl, pyridylmethyl, phenethyl or thienyl group, or R_4 represents a substituted phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl group wherein the aromatic rings are substituted with 1, 2 or 3 of the substituents Y, wherein Y has the meaning as indicated above,

or when R_3 is H or methyl, R_4 may represent a group NR_6R_7 wherein

- R_6 and R_7 are the same or different and represent C_{2-4} alkyl , C_{2-4} trifluoroalkyl or R_6 represents a methyl group with the proviso that R_7 represents a C_{2-4} alkyl group, or R_6 and R_7 - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated heterocyclic moiety having 4 to 8 ring atoms which heterocyclic moiety may contain an oxygen or sulphur atom or a keto group or $-SO_2-$ group or an additional nitrogen atom, which saturated or unsaturated heterocyclic moiety may be substituted with a C_{1-4} alkyl group, or
- R_3 and R_4 together with the nitrogen atom to which they are bonded form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms, which heterocyclic moiety may contain one or more atoms from the group (O, N, S) or a keto group or $-SO_2-$ group, which moiety may be substituted with a C_{1-4} alkyl, hydroxyalkyl, phenyl, thienyl, pyridyl, amino, monoalkylaminoalkyl, dialkylaminoalkyl, monoalkylamino, dialkylamino, aminoalkyl, azetidinyl, pyrrolidinyl, piperidinyl or hexahydro-1H-azepinyl group,
- R_5 represents benzyl, phenyl, thienyl or pyridyl which may be substituted with 1, 2, 3 or 4 substituents Y, wherein Y has the meaning as indicated above, which can be the same or different, or R_5 represents C_{1-8} branched or unbranched alkyl, C_{3-8} alkenyl, C_{3-10} cycloalkyl, C_{5-10} bicycloalkyl, C_{6-10} tricycloalkyl or C_{5-8} cycloalkenyl or R_5 represents naphtyl.

and tautomers, prodrugs, stereoisomers and salts thereof.

2. Pharmaceutical compositions containing a pharmacologically active amount of at least one compound as claimed in claim 1 as an active component.

3. Method of preparing pharmaceutical compositions as claimed in claim 2 characterised in that a compound as claimed in claim 1 is brought in a form suitable for administration.

4. Use of a compound as claimed in claim 1 for the preparation of a pharmaceutical composition for the treatment of disorders involving cannabinoid neurotransmission.

5. Use as claimed in claim 4 characterised in that said disorders are psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetence, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral

ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelinisation related disorders, as well as for the treatment of pain disorders, including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/10433

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/415 C07D231/06 C07D401/12 A61K31/4155 C07D401/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 70700 A (SOLVAY PHARMACEUTICALS B V) 27 September 2001 (2001-09-27) see the formula (i) definition for Aa the whole document	1-5
A	US 5 624 941 A (BARTH FRANCIS ET AL) 29 April 1997 (1997-04-29) the whole document	1-5
A	US 4 070 365 A (VAN DAALEN JAN JOHANNES ET AL) 24 January 1978 (1978-01-24) the whole document	1-5

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 November 2002	29/11/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PERTWEE R G: "PHARMACOLOGY OF CANNABINOID RECEPTOR LIGANDS" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 6, no. 8, August 1999 (1999-08), pages 635-664, XP000923352 ISSN: 0929-8673 cited in the application see page 641	1-5
A	WO 00 46209 A (SANOFI SYNTHELABO ;BARTH FRANCIS (FR); CAMUS PHILIPPE (FR); MARTIN) 10 August 2000 (2000-08-10) the whole document	1-5

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0170700 A	27-09-2001	AU 4250101 A	03-10-2001
		WO 0170700 A1	27-09-2001
		US 2001053788 A1	20-12-2001
US 5624941 A	29-04-1997	FR 2692575 A1	24-12-1993
		FR 2713224 A1	09-06-1995
		FR 2713225 A1	09-06-1995
		AT 149489 T	15-03-1997
		AU 4143893 A	06-01-1994
		BR 1100409 A3	13-10-1999
		BR 9302435 A	11-01-1994
		CA 2098944 A1	24-12-1993
		CZ 9301172 A3	16-03-1994
		DE 69308395 D1	10-04-1997
		DK 576357 T3	15-09-1997
		EP 0576357 A1	29-12-1993
		ES 2101258 T3	01-07-1997
		FI 932891 A	24-12-1993
		GR 3023535 T3	29-08-1997
		HU 64526 A2	28-01-1994
		IL 106099 A	15-07-1998
		JP 3238801 B2	17-12-2001
		JP 6073014 A	15-03-1994
		MX 9303664 A1	31-01-1994
		NO 932296 A	27-12-1993
		NZ 247961 A	28-08-1995
		RU 2119917 C1	10-10-1998
		SK 65493 A3	02-02-1994
		ZA 9304511 A	22-02-1994
		AT 154012 T	15-06-1997
		AU 685518 B2	22-01-1998
		AU 7899994 A	15-06-1995
		BR 1100984 A3	14-03-2000
		CA 2136893 A1	21-06-1995
		CN 1110968 A ,B	01-11-1995
		CZ 9403016 A3	14-06-1995
		DE 69403614 D1	10-07-1997
		DE 69403614 T2	22-01-1998
		DK 656354 T3	29-12-1997
		EP 0656354 A1	07-06-1995
		ES 2105575 T3	16-10-1997
		FI 945690 A	03-06-1995
		GR 3024470 T3	28-11-1997
		HK 1000599 A1	09-04-1998
		HU 71498 A2	28-11-1995
		IL 111719 A	28-10-1999
		JP 3137222 B2	19-02-2001
		JP 7309841 A	28-11-1995
		JP 2001026541 A	30-01-2001
		NO 944625 A	06-06-1995
		NZ 270025 A	26-09-1995
		PL 306067 A1	12-06-1995
		RU 2141479 C1	20-11-1999
		SG 68570 A1	20-06-2000
US 4070365 A	24-01-1978	NL 7409433 A	14-01-1976
		AR 223449 A1	31-08-1981
		AT 359775 B	25-11-1980

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int[redacted]ional Application No
PCT/EP 02/10433

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 4070365 A		AT	508277 A	15-04-1980
		AT	342585 B	10-04-1978
		AT	529175 A	15-08-1977
		AU	501280 B2	14-06-1979
		AU	8285075 A	13-01-1977
		BE	831232 A1	12-01-1976
		BR	7504413 A	06-07-1976
		CA	1075242 A1	08-04-1980
		CH	624675 A5	14-08-1981
		CS	188962 B2	30-03-1979
		DD	122775 A5	05-11-1976
		DE	2529689 A1	29-01-1976
		DK	310975 A ,B,	13-01-1976
		EG	11880 A	30-09-1978
		ES	439292 A1	16-02-1977
		FR	2277827 A1	06-02-1976
		GB	1514285 A	14-06-1978
		HU	178320 B	28-04-1982
		IE	41836 B1	09-04-1980
		IL	47676 A	31-01-1979
		IT	1044358 B	20-03-1980
		JP	1368569 C	11-03-1987
		JP	51041358 A	07-04-1976
		JP	61023162 B	04-06-1986
		OA	5057 A	31-12-1980
		PL	105891 B1	30-11-1979
		PL	193676 A1	17-07-1978
		SE	419644 B	17-08-1981
		SE	7507868 A	13-01-1976
		US	4156007 A	22-05-1979
		YU	176475 A1	30-06-1982
		ZA	7504203 A	23-02-1977
WO 0046209 A	10-08-2000	FR	2789078 A1	04-08-2000
		FR	2789079 A1	04-08-2000
		AU	2298900 A	25-08-2000
		BG	105749 A	28-02-2002
		BR	0007895 A	30-10-2001
		CN	1346349 T	24-04-2002
		CZ	20012697 A3	17-10-2001
		EE	200100399 A	15-10-2002
		EP	1150961 A1	07-11-2001
		WO	0046209 A1	10-08-2000
		HR	20010564 A1	31-08-2002
		NO	20013736 A	28-09-2001
		NZ	512886 A	25-10-2002
		SK	10872001 A3	03-12-2001
		TR	200102054 T2	21-05-2002
		US	6432984 B1	13-08-2002